

Validity of Estimated Glomerular Filtration Rate Equation and Assessment of Bio-Impedance Analysis in Advanced Chronic Kidney Disease Patients

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Abstract

Introduction: This cross-sectional study was conducted to validate estimated glomerular filtration rate (eGFR) equation and assess body composition in chronic kidney disease (CKD) stage 5 non-dialysis (ND) participants.

Methods: A total of 111 samples of Thai CKD stage 5 ND participants with eGFR below 15 mL/min/1.73 m², calculated by using the CKD Epidemiology Collaboration (CKD-EPI) equation, were enrolled into the study. The 99mTc-DTPA plasma clearance was used as the reference GFR. Body composition analysis was measured by bio-impedance analysis (BIA) to assess volume as well as body composition.

Results: The mean isotope for GFR was 17.39±6.83 mL/min/1.73m². The mean bias values between isotope GFR and re-expressed MDRD equation, CKD-EPI equation, Thai equation, and cystatin C-based equation were 8.89±6.35, 9.47±6.13, 2.05±6.80, and 5.50±6.40 mL/min/1.73m², respectively. The accuracy (root-mean-square error) values were 13.05, 13.68, 8.73, and 10.58 mL/min, respectively. Using BIA, the low muscle mass was 33.66%, excessive fat was 55.00 %, and the presence of edema was 48.5%. Participants with low muscle mass, excessive fat, and subclinical edema had higher bias of GFR measurement for all equations. The bias values for eGFR in participants with low muscle mass, excessive fat, and subclinical edema by re-expressed MDRD equation were 10.23, 9.61, 10.88 mL/min/1.73m²; by CKD-EPI equation: 8.49, 10.25, 11.63 mL/min/1.73m²; by the Thai eGFR equation: 3.16, 2.73, 4.77 mL/min/1.73m²; and by the cystatin C-based equation: 6.32, 6.6, 7.99 mL/min/1.73m², respectively.

Conclusions: The Thai equation was the most accurate and precise method to determine the renal function of Thai CKD stage 5 ND participants who had a high prevalence of low muscle mass, excessive fat, and subclinical edema. The result suggested that ethnic-specific eGFR equation should be recommended in advanced CKD patients. Alteration of the body composition in advanced CKD patients is of concern because it can affect the performance of all of the eGFR equations.

Introduction

The numbers of chronic kidney disease (CKD) patients have been incessantly increasing worldwide¹. Initiation of renal replacement therapy (RRT) in CKD stage 5 patients requires many resources and has high healthcare expenditures². Manifestations of end-stage renal disease (ESRD) with uremic symptoms occur when uremic toxin excretory function is severely impaired, which generally occur at very low glomerular filtration rate (GFR), and RRT initiation is mandatory to save life. Early RRT initiation in asymptomatic advanced CKD patients prevents uremic symptoms; however, too early initiation could lead to increased mortality and morbidity³. Earlier initiation of RRT in advanced CKD patients not only cause deleterious effects to the patients, but also incurs a large burden on the healthcare budget. It is challenging to circumvent both extreme situations in clinical practice, especially when to initiate RRT in asymptomatic CKD stage 5 patients.

Isotope-derived GFR is currently utilized as the gold standard method in measuring GFR but is not widely available⁴. Estimated GFR (eGFR) obtained from various equations has been used in clinical setting. Unfortunately, current eGFR equations such as The Modification of Diet in Renal Disease (MDRD)⁵, CKD Epidemiology Collaboration (CKD-EPI)⁶ equations, and racial-specific derived eGFR equations have never been validated in advanced CKD patients, especially to provide guidance when RRT should be initiated. Furthermore, advanced CKD patients commonly encounter malnutritional status⁷ which may alter serum creatinine level and consequently affect eGFR value when applied to serum creatinine-based eGFR equations. Therefore, validation of various GFR-estimating equations in advanced CKD, especially to make a verdict when dialysis should be started, is crucially needed.

In the present study, the recommended serum creatinine-based eGFR equations and cystatin C-based eGFR equation were validated with isotope GFR in CKD stage 5 non-dialysis (ND) participants. Body composition analysis was performed to determine the volume status as well as nutritional conditions.

Materials And Methods

Study population

Stable advanced CKD patients who were older than 18 years old with eGFR below 15 mL/min/1.73m², as calculated by the CKD-EPI equation, were recruited into the study. CKD was diagnosed and classified according to the KDIGO guideline. The study was conducted in an ambulatory setting and started at 08:00–09:00 AM in order to avoid the diurnal variations of the renal function. Patients having the following conditions were excluded from the study: acute deterioration of the renal function, amputation, bedridden state, infection, gastrointestinal bleeding, and heart failure or hospitalization. Women of childbearing age without a reliable contraceptive method, patients on RRT, and patients taking methyl dopa, levodopa, ascorbic acid, cimetidine, trimethoprim, antibiotics, steroids, or flucytosine were also excluded.

Reference GFR measurement

The reference GFR was determined by collecting plasma from 10 different time points and was subjected to 99mTc- Diethyle Triamine Penta-acetic Acid (99mTcDTPA) plasma clearance method, which was performed at the Department of Radiology, Chulalongkorn University. 99mTc-DTPA was purchased from the Office of Atoms for Peace, Bangkok, Thailand, with a radiopurity of >95% and 99mTc-DTPA bound to plasma protein of <5%. The same protocol was applied to all participants. In brief, heparin lock was inserted into the arm to obtain blood samples to determine the radioactivity background and for serum creatinine assay. A single intravenous bolus of 99mTc-DTPA was injected into each participant. Blood specimens were collected to assess plasma radioactivity at 5, 10, 15, 20, 30, 60, 90, 120, 180, and 240 minutes post 99mTc-DTPA injection. Plasma radioactive activities were then plotted as a function of time to create a time-activity curve in order to calculate the GFR. The GFR equation was determined using bi-exponential fitting method that was utilized in a previous study⁸.

Calibration for serum creatinine assay and laboratory measurement of Cystatin C

Fasting serum creatinine was measured using CREA plus (11775642) enzymatic assay[®] on a COBAS INTEGRA 400 plus analyzer, Roche Diagnostics (Indianapolis, IN), traceable to isotope-dilution mass spectrometry, as recommended by the National Kidney Disease Education Program⁹. The IDMS reference serum creatinine (SRM 967) was purchased from the National Institute of Standards and Technology. The certified concentration values of serum creatinine were 0.847 ± 0.018 mg/dL for level 1 and 3.877 ± 0.082 mg/dL for level 2. Cystatin C was measured by Biovendor human cystatin C ELISA kit[®] (RD191009100) (Candler, NC) which has been recommended for in vitro diagnostic use by the European Union.

eGFR calculation

The eGFR values were calculated using the re-expressed MDRD equation¹⁰, CKD-EPI equation⁶, Thai eGFR equation⁸, and cystatin C-based eGFR equation¹¹ (supplementary data table S1).

Body composition analysis

Bioelectrical impedance analysis (BIA) by Inbody[®] 720 Body Composition Analyzer (Biospace, Seoul, Korea) was used to measure the body composition such as weight, fluid, muscle, and fat. This method utilized the tetrapolar eight-point tactile electrode system. Thirty impedance measurements were gathered using six different frequencies (1, 5, 50, 250, 500, and 1000 kHz) at each of the five segments of the body: right arm, left arm, trunk, right leg, and left leg. Reactance was performed utilizing 15 impedance measurements using the three frequencies (5, 50, and 250 kHz) at each of the five segments of the body. Bioelectrical impedance measurements were performed after the blood samples were collected.

Statistical analysis

Bland–Altman plots were used to assess the agreement between eGFR from various equations and the reference GFR. The regression of the average and the difference between the reference GFR and the eGFR (reference GFR minus eGFR) were analyzed. Bias was defined as the mean absolute difference between the reference and eGFR. Precision was defined as the standard deviation value of the mean absolute difference. Accuracy was defined as the proximity of the estimation compared with the reference and was calculated using combined root mean square error and the percentage of GFR within 30% of the reference GFR. Root mean square error (RMSE) was calculated to estimate the spread out of the predicting error. The accuracy of the equation was compared by the χ^2 test. Statistical analysis was performed by using SPSS for windows version 22.0.

Ethics approval and informed consent

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (Bangkok, Thailand; IRB.644/59), approved the study. Information pertaining to the study was provided to all interested

participants prior to obtaining their written informed consent.

Results

Characteristics of the participants

One hundred and eleven participants were enrolled into the study. The mean age of the participants was 59.4 ± 17.5 years and 40% were male. The average reference eGFR calculated by CKD-EPI equation and serum creatinine were 8.16 ± 3.63 mL/min/1.73m² and 6.79 ± 3.02 mg/dL, respectively. All participants were in stable condition. Hypertension and diabetic nephropathy were the two major causes of CKD. All participants had sub-nephrotic range of proteinuria. Demographic characteristics and laboratory data of the study population are shown in Table 1.

Body composition analysis

One hundred and one participants had bioelectrical impedance results. The mean skeletal muscle mass was 22.92 ± 5.94 kg and the mean skeletal muscle mass index (SMMI) was 8.95 ± 1.64 kg/m². The percentage of the participants with low muscle mass was 33.66%. Low muscle mass was based on the criteria reported in the Asian population study¹². The mean total body fat was 15.40 ± 10.72 kg and the mean percentage of the total fat was 27.06. Fifty-five percent of the participants had excessive fat. The mean extracellular water/total body water was 0.40 ± 0.01 . Edema was detected in 48.51 % of the participants using BIA.

Assessing agreement between eGFR values from different equations and the reference GFR

The mean isotope GFR was 17.39 ± 6.83 mL/min/1.73m². The mean estimated GFR values by re-expressed MDRD, CKD-EPI, Thai eGFR, and cystatin C-based eGFR equations were 8.61 ± 3.89 , 8.16 ± 3.63 , 15.69 ± 5.51 , and 12.46 ± 3.6 mL/min/1.73m², respectively.

To assess the agreement between eGFR values and the reference GFR, Bland–Altman plots were produced (Figure 1A-D). A comparison of the agreement was evaluated by calculating the bias which was estimated based on the mean differences and the limits of agreement of each eGFR equation. The mean bias values between isotope GFR and re-expressed MDRD equation, CKD-EPI equation, Thai equation, and cystatin C-based eGFR equation were 8.89 ± 6.35 , 9.47 ± 6.13 , 2.05 ± 6.80 , and 5.50 ± 6.40 mL/min/1.73m², respectively.

The Thai eGFR equation was the most accurate equation, the percentage of estimates within 30% of the isotope GFR (P30) was 57.4%, followed by cystatin C-based (44.1%), MDRD (13.8%), and CKD-EPI eGFR equations (12%) (Table 2).

Performance of eGFR equation in low muscle mass, excessive fat mass, and edematous state in advanced CKD participants

The prevalence of low muscle mass in advanced CKD participants was 33.66 %. In this group, all eGFR equations had higher bias, lower precision, and lower accuracy by P30 than CKD participants with normal muscle mass. Of these, the Thai eGFR equation had the lowest mean bias (3.16 ± 7.73 mL/min/ 1.73m^2) and highest accuracy (P30 = 47.6%) compared to other eGFR equations (Table 2). This indicated that the Thai eGFR equation's performance was significantly precise and accurate in Thai advanced CKD participants.

Fifty-eight percent of the CKD participants had excessive fat mass. In this group, all of the eGFR equations had higher bias than CKD participants with normal fat mass. Of these, the Thai eGFR equation still had the lowest mean bias (2.73 ± 5.71 mL/min/ 1.73m^2) and the highest accuracy (P30 = 65.6%) compared to other eGFR equations (Table 2).

Forty-eight percent of the advanced CKD participants had an edematous state by BIA. The mean bias of all eGFR equations increased in CKD participants with edema compared to those without edema. The Thai eGFR equation had the lowest bias in the edematous state (4.77 mL/min/ 1.73m^2) and was the most accurate (P30 = 56.7%) compared to other eGFR equations (Table 2).

Discussion

This cross-sectional study validated eGFR equations, including serum creatinine-based and cystatin C-based eGFR equations, in CKD stage 5 ND participants. Isotope GFR was used as the reference GFR. We described that the Thai ethnicity eGFR equation provided the best accuracy and precision in Thai advanced CKD participants compared to other eGFR equations derived from Caucasian and African-American populations. Furthermore, we demonstrated that the alteration of the body composition in advanced CKD participants affected the precision and accuracy of all eGFR equations. Despite this, the Thai eGFR equation still provided the best performance in Thai advanced CKD participants with low muscle mass, excessive fat, and edematous state.

The decision to initiate RRT in CKD stage 5 patients is challenging in clinical practice. Typical uremic symptoms, including pericarditis and encephalopathy, were clear indications for initiating RRT; however, it is challenging to decide when to initiate RRT in asymptomatic CKD stage 5 patients. If RRT is started too early, then the patients are unnecessarily exposed to hemodialysis complications. As a matter of fact, other uremic manifestations are frequently nonspecific and can be originated from other non-renal causes. Moreover, these asymptomatic advanced CKD patients may not have obvious clinical manifestations, so other means are necessary to ascertain these patients' renal function. eGFR is one of the objective indicators to represent an excretory function in CKD patients. Previous clinical practice guidelines recommended starting RRT at higher eGFR cut-off values^{13, 14}. With such recommendations and the belief that early RRT initiation might prevent the progressive decline in nutritional status, the proportion of CKD patients initiating RRT at higher GFR has been increasing over the past decade. Unfortunately, there is no definitive evidence to support this approach; recent clinical

studies and meta-analysis reported that RRT initiation at higher GFR using the Cockcroft-Gault and MDRD equations was associated with higher mortality rate¹⁵.

Serum creatinine is the most common marker used to estimate the kidney function in current practice. However, several well-documented factors affected serum creatinine, including age, sex, ethnicity, and muscle mass¹⁶. All available creatinine-based eGFR equations were highly influenced by the muscle mass. Approximately 28.7-65.5% of advanced CKD patients had reduced muscle mass¹⁷, possibly resulting in inaccurate and overestimated eGFR levels. On the other hand, serum cystatin C, a product of an endogenous gene, has been suggested to be able to overcome the limitation of serum creatinine from the effect of muscle mass in the evaluation of the kidney function.

There are two most commonly used creatinine-based eGFR formulae: the re-expressed MDRD and the CKD-EPI equations. These two equations have not been validated in advanced CKD populations that have higher incidence of sarcopenia and other chronic illnesses. According to MDRD and CKD-EPI dataset, 25% of the subjects with eGFR < 15 ml/min per 1.73 m² had measured GFR values > 15 ml/min per 1.73 m². Most of these were in the range of 15–29 ml/min per 1.73 m²⁶. This means that some patients were over-diagnosed as CKD stage 5 and might have inappropriately started RRT. Furthermore, the re-expressed MDRD and the CKD-EPI equations were primarily developed for Caucasian and African-American CKD populations. A previous study showed that Asians have a higher percentage of body fat and lower levels of muscle mass for the same BMI level than Caucasians¹⁸; this suggests that ethnicity can interfere with the calculation for eGFR and that there is a need to validate eGFR equations in non-Caucasian and non-African-American advanced CKD patients.

In the present study, the Thai eGFR equation was the least biased equation with the most precision and accuracy followed by the cystatin C-based equation. In comparison, the re-expressed MDRD and CKD-EPI equations showed higher bias with a tendency to underestimate eGFR (mean error 8.89 ml/min/1.73m² and 9.49 ml/min/1.73m² according to the re-expressed MDRD equation and CKD-EPI equation, respectively; Figure1). It would mean that all of our advanced CKD participants (CKD stage 5 by CKD-EPI) would then have to start RRT too early which could result in detrimental medical consequences, waste of resources, and have exorbitant health care costs.

In a low muscle mass setting, which was approximately one-third of the participants in this study, all eGFR equations had more bias and lower accuracy. Likewise, excessive fat and edematous state also tended to decrease the performance of the equations because these patients usually have lower muscle mass than other patients with the same BMI. These results emphasized the importance of body composition of advanced CKD patients because it can affect the performance of the eGFR equations. The measurement of serum cystatin C was favorable in low serum creatinine production conditions, especially among patients with malnutrition or amputation. Theoretically, the cystatin C-based eGFR equation should be less affected by anthropometry and body composition. However, a previous study reported that fat mass was associated with cystatin C elevation independently of reduced GFR¹⁹. In the

present study, the cystatin C-based equation actually improved GFR estimation performance compared to the re-expressed MDRD and CKD-EPI equations. Nonetheless, our results showed that the cystatin C-based equation still had lower precision and accuracy than the Thai eGFR equation, possibly due to ethnicity differences during this equation's standardization. Therefore, it is recommended that a specific eGFR equation should be developed based on the ethnicity for advanced CKD patients with either normal or low muscle mass status, such as the Thai eGFR equation.

Since the body composition of advanced CKD patients affects the performance of all eGFR equations, hence we suggest that body composition analysis should be performed in this population which provides not only nutritional status data but also provides essential information that can correct the assessment for eGFR.

Our findings indicated that an ethnic-specific eGFR equation and body composition analysis are essential in CKD stage 5 patients. This information is helpful and can effectively guide the clinicians to provide proper treatment to all advanced CKD patients, including the most appropriate time to start RRT. Even though we are the first group to simultaneously validate the eGFR equations, identify subclinical edematous state, and assess body muscle and fat mass in CKD stage 5 participants, yet there were some limitations in our study. We acknowledge that the sample size was small. Second, due to the study's design, we could not examine the relationship between eGFR and other conditions such as muscle mass, fat mass, and subclinical edematous status. Future studies conducted at various time points are warranted to assess when it is the most appropriate time to initiate RRT in asymptomatic CKD stage 5 patients.

In conclusion, the eGFR by the Thai equation provided the most accurate and precise information of the renal function of Thai advanced CKD patients even when there was a high prevalence of low muscle mass, excessive fat, and subclinical edema. These findings emphasize the importance of having an ethnic-specific eGFR equation which can provide beneficial guidance for optimal treatment and RRT initiation in patients with advanced CKD. Alteration of the body composition in advanced CKD patients are of concern because it can affect the performance of all eGFR equations. Therefore, body composition analysis should be recommended for all advanced CKD patients.

Abbreviations

95% CI: 95% confidence interval; BCM: Body cell mass; BIA: Bio-impedance analysis

BMI: Body mass index; CKD: Chronic kidney disease; DTPA: Diethyle Triamine Penta-acetic Acid; eGFR: Estimated glomerular filtration rate; EPI: Epidemiology Collaboration; ESRD: End-stage renal disease; MDRD: Modification of Diet in Renal Disease; ND: non-dialysis;

OH: Overhydration; RMSE: Root mean square error; RRT: renal replacement therapy

SD: Standard deviation; SMMI: Skeletal muscle mass index

Declarations

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Authors' contributions

Study design: K.Ta., T.C., P.S., K.P.

Data collection: T.C., P.S., K.P.

Data analysis: K.Ta., P.S., K.P.

Data interpretation: K.Ta., P.S., P.Ki., P.Ka., S.E., K.P.

Writing: K.Ta., T.C., P.S., P.Ki., P.Ka., K.Ti, K.Tu, S.E., K.P.

Figure: K.Ta., K.P.

All authors contributed to the final draft.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study complies with the principles of the Helsinki Declaration 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO). The whole protocol has been reviewed and approved by the Ethical Committee, Chulalongkorn University, Bangkok, Thailand (IRB. Number 644/59). Written informed consent was obtained from all patients included in the study.

Consent for Publication

All authors consent to the publication of this manuscript.

Competing interests

All authors declare that they have no conflict of interest.

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Tables

Table 1. Clinical and laboratory parameters.

Characteristics	
Age (year)	59.4±17.5
Sex: Male/Female (%)	31.9%/68.1%
Body weight (Kg)	61.26±15.18
Body mass index (Kg/m²)	24.15±5.33
Co-morbidities	
Hypertension	73.91%
Diabetes mellitus	39.70%
Dyslipidemia	42.04%
Cardiovascular disease	13.05%
Causes of chronic kidney disease	
Hypertensive nephrosclerosis	42.04%
Diabetic nephropathy	23.19%
Chronic glomerulonephritis	1.45%
Obstructive uropathy	1.45%
Unknown	31.87%
Current medication	
HMG-CoA reductase inhibitor	42.04%
Beta-blocker	23.19%
ACEI/ARB	7.24%
BUN (mg/dL)	65.96±18.50
Creatinine (mg/dL)	6.79±3.02
Cystatin C (mg/L)	4.18±0.97
Urine volume (mL/day)	1,828±903.25
Urine protein (g/day)	1.98±1.71
Hemoglobin (g/dL)	10.3±1.6
High sensitivity C-reactive protein*(mg/L)	4.79 (2.37, 7.86)
Albumin (g/dL)	4.02±0.49
Uric acid (mg/dL)	8.8±9.4

Total cholesterol (mg/dL)	191.6±58.0
Triglyceride (mg/dL)	149.9±77.8
Fasting blood sugar (mg/dL)	90.1±25.0
Skeletal muscle mass	
Male/Female (kg)	29.03±4.60/20.01±3.98
Skeletal muscle mass index (SMMI)	
Male/Female (kg/m ²)	10.21±1.42/8.06±1.46
Total body fat: Male/Female (%)	20.26±12.94/26.22±13.95
ECW/TBW	0.40±0.01
BIA-edema** (%)	48.38%

Data are presented as %, mean±SD, or *median (IQR).

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BIA, body composition analysis; BUN, blood urea nitrogen; ECW, extracellular water; HMG-CoA, hydroxymethylglutaryl-coenzyme A; ICW, intracellular water; SGPT, serum glutamine pyruvate transaminase; TBW, total body water

**BIA-edema was defined as ECW/TBW more than 0.4

Table 2. Performance of eGFR equation in advanced CKD participants with low muscle mass, excessive fat mass, and edema.

	Reference mGFR (99mTcDTPA)	Re- expressed MDRD equation	CKD-EPI equation	Thai eGFR equation	Cystatin C- based equation
Mean eGFR (mL/min/1.73m ²)	17.39±6.83	8.61±3.89	8.16±3.63	15.69±5.51	12.46±3.6
Bias	N/A	8.89	9.47	2.05	5.5
Precision (SD of bias)	N/A	6.35	6.13	6.80	6.40
Accuracy P ₃₀ (%)	N/A	13.8	12	57.4	28.8
RMSE	N/A	10.96	11.17	7.87	9.57
Low muscle mass (n= 34)					
Bias	N/A	10.23	8.49	3.16	6.32
Precision (SD of bias)	N/A	6.97	5.37	7.73	7.53
Accuracy P ₃₀ (%)	N/A	14.2	14.2	47.6	18.2
RMSE	N/A	9.53	9.75	7.71	6.79
Excessive fat (n=57)					
Bias	N/A	9.61	10.25	2.73	6.60
Precision (SD of bias)	N/A	5.38	5.39	5.71	5.7
Accuracy P ₃₀ (%)	N/A	12.5	12.5	65.6	27.6
RMSE	N/A	10.97	11.54	6.26	8.27
Edema (n=50)					
Bias	N/A	10.88	11.63	4.77	7.99
Precision (SD of bias)	N/A	7.42	7.33	7.43	7.52
Accuracy P ₃₀ (%)	N/A	9.1	6.1	56.7	15.6
RMSE	N/A	13.05	13.68	8.73	10.58

Figures

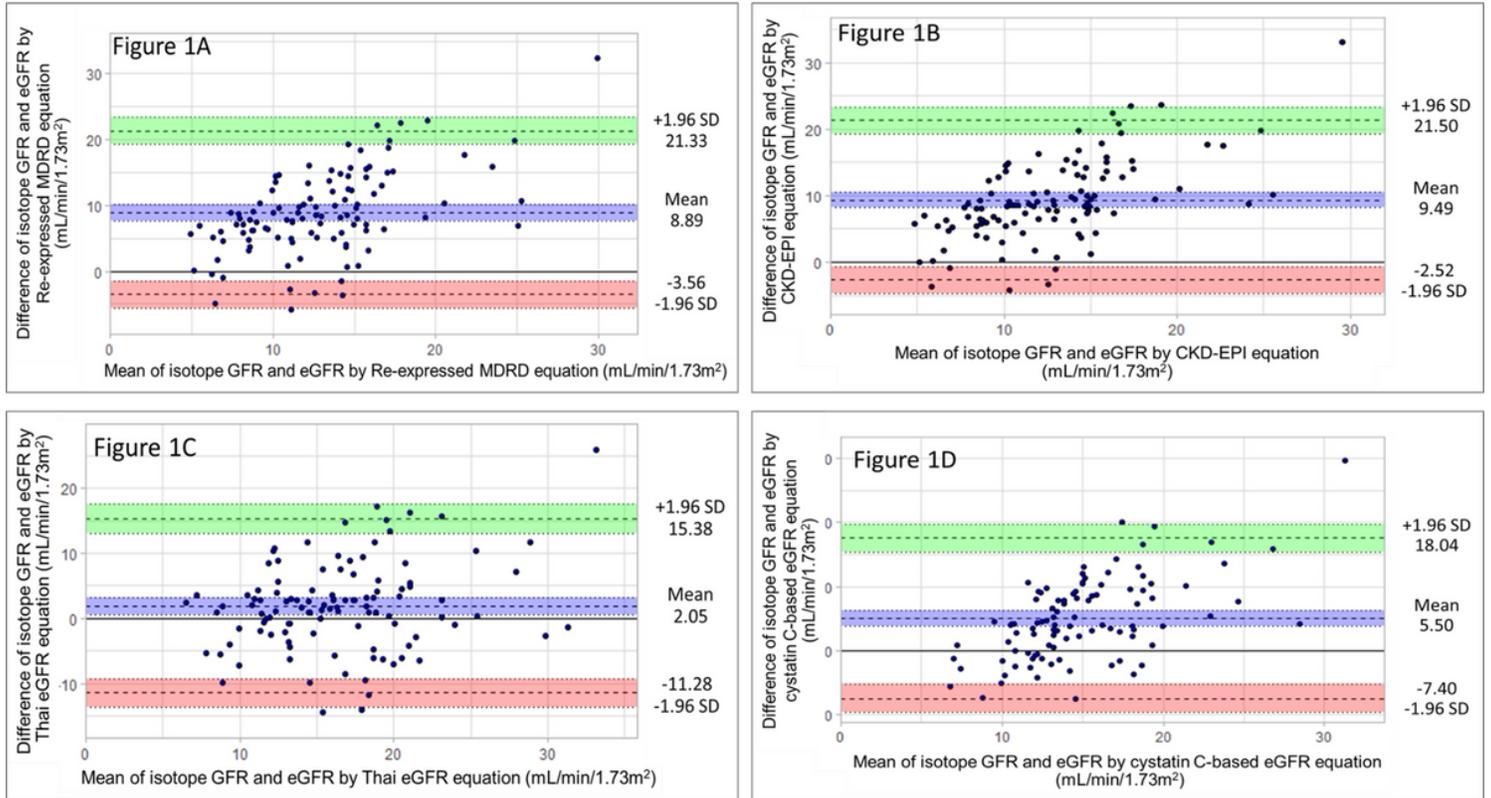


Figure 1

Bland-Altman plots of eGFR values calculated by different eGFR equations and the reference GFR. The disagreement of different equations [A; re-expressed MDRD equation, B; CKD-EPI equation, C; Thai eGFR equation, D; cystatin C-based eGFR equation] are shown as the mean bias of the eGFR towards the reference GFR \pm 1.96 standard deviation (horizontal line).

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